

Remarks/Arguments:

New claims 61-83 are presented, hereby.

Claims 38-60 are canceled, hereby, without prejudice or disclaimer.

Present claim 61 contains the subject matter of claim 38, amended (1) to recite "a pH of 8 to 12" (described in the specification at page 7, ¶1), instead of a pH > 8, and (2) to recite the "chaotropic substance" is "present at a concentration of 4-9 M" (as described in the specification at page 14, ¶2).

Present claims 62-83 correspond to claims 39-60, revised to depend directly or indirectly on present claim 61.

Claims 38-60 were rejected under 35 USC 112, ¶1, for allegedly lacking enablement "for using any chaotropic agent at a pH over 8 to separate plasmid DNA from RNA and linear DNA" (Office Action, page 3). Reconsideration is requested in view of the changes to the claims effected, hereby, in conjunction with the following remarks.

The present claims are limited to a pH of 8-12, i.e., they are no longer limited to *any* pH over 8, set forth in the statement of rejection as having a scope broader than the enablement provided in the instant specification. Since the present claims do not reflect the scope allegedly too broad for the scope of enablement provided, the rejection under § 112, ¶1, is overcome and withdrawal of the rejection is, therefore, in order.

Claims 38-47 and 50-58 were rejected under 35 USC 112, ¶2, for allegedly being indefinite for reciting the terminology "crude bacterial lysate." Reconsideration is requested.

The §112, ¶2, rejection is maintained despite the *law* set down in precedential decisions by the Court of Appeals for the Federal Circuit ("Federal Circuit"), which precedent is *binding* on the examiner in the instant matter. The meaning of the terminology at issue cannot be determined in a vacuum; words in the specification are properly used *during prosecution* as an aid in interpreting *existing* claim limitations. *In re Donaldson Co. Inc.*, 29 USPQ2d 1845, 1850 (Fed. Cir. 1994). It is abundantly clear from the present specification what is meant by "crude bacterial lysate"; the material resulting from lysing bacteria is not purified in any way. This, therefore, is the meaning of the terminology that must be used by the Examiner. The Examiner's definition of a claim limitation cannot conflict with the definition given in the specification. *In re Zletz*, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989). The Examiner must use the specification definition in construing the claims for comparison with the prior art.

When the applicant states the meaning that the claim terms are intended to have, the claims are examined with that meaning, in order to achieve a complete exploration of the applicant's invention and its relation to the prior art.

Zletz, 13 USPQ2d at 1322. Accordingly, the rejection is in order for withdrawal.

Claims were rejected under 35 USC 103(a) based on the combined teachings of Little and Marko, based on the combined teachings of Little, Marko, Smith, and Segel, and based on the combined teachings of Bastian (either the U.S. patent or the corresponding published International application) and Segel. Reconsideration is requested with respect to the aforesaid rejections.

Withdrawal of the rejections of record under §103(a) is in order for the reasons of record as set forth in the Amendment filed September 17, 2002, in the PTO. For the convenience of the Examiner, the reasons are repeated, below.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). When conducting an obviousness analysis, "all limitations of a claim must be considered in determining the claimed subject matter as is referred to in 35 U.S.C. 103 and it is error to ignore specific limitations distinguishing over the [prior art] reference." *Ex parte Murphy*, 217 USPQ 479, 481 (PO Bd. App. 1982).

In the context of a rejection for obviousness under §103, the "*Examiner* bears [both] the initial burden . . . of presenting a *prima facie* case of unpatentability" and "the ultimate burden of persuasion on the issue." *In re Oetiker*, 24 USPQ 1443, 1444 and 1447 (Fed. Cir. 1992), *emphasis, added*.

The "evidence upon which the examiner relies must clearly indicate that a worker of routine skill in this art would view the claimed invention as being obvious." *Ex parte Wolters*, 214 USPQ 735, 736 (BPA&I 1982). "It is facts which must support the legal conclusion of obviousness." *Ex parte Crissy*, 201 USPQ 689, 695 (POBdApp 1976).

The Patent Office has the initial duty of supplying the factual basis for its rejection. It may not, because *it may doubt* that the invention

is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in the factual basis.

In re Warner, 154 USPQ 173, 178 (CCPA 1967) (*emphasis in original*). An argument by the USPTO is "not prior art." *In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). When the

USPTO asserts that there is an explicit or implicit teaching or suggestion in the prior art, it must indicate where such a teaching or suggestion appears *in the reference*. . . . The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient to establish inherency. . . . [S]uch a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection.

28 USPQ2d at 1557, *emphasis added*.

When the claimed invention requires modification of the prior art, there is no obviousness under §103 when "[t]he prior art does not suggest . . . modification of the . . . [prior art], or provide any reason or motivation to make the modification." *In re Laskowski*, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989).

"The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art *would lead* that individual to combine the relevant references. . . . Indeed, the teachings of the references can be combined only if there is some suggestion or incentive to do so." *Ex parte Obukowicz*, 27 USPQ 1063, 1065 (BPA&I 1992)(*emphasis, added*).

As explained by the Board in the decision *Ex parte Levengood*, 28 USPQ2d 1300, 1300-01 (BPA&I 1993)(*emphasis in original*):

In order to establish a *prima facie* case of obviousness, it is necessary for the examiner to present *evidence*,^[1] preferably in the form of some teaching, suggestion, incentive or inference in the applied prior art, that one having ordinary skill in the art *would have been led* to combine the relevant teachings of the applied references in the proposed manner to arrive at the claimed invention [*citations, omitted*].

The fact that all elements of a claimed invention are known does not, by itself, make the combination obvious. *Ex parte Clapp*, 227 USPQ 972 (BPA&I 1985). To support a rejection for obviousness based on the combination of separate prior art teachings, the USPTO "must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination." *In re Rouffet*, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998).

"One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

It is impermissible within the framework of §103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.

In re Hedges, 228 USPQ 685, 687 (Fed. Cir. 1986).

To reject claims for obviousness under §103 based on modifying the teachings of a reference, existence in the prior art of a reason (motivation) to effect the modification is not, by itself, sufficient to sustain the initial burden on the PTO; the "record" must show

. . . that it would also have been obvious *how* this [modification] could be achieved . . . Obviousness . . . must not be judged by hindsight, and a "little modification" can be a most unobvious one.

In re Irani, 166 USPQ 24, 27 (CCPA 1970) (*emphasis in original*).

The statement of rejection takes the point of view that the determination of a suitable pH range for practice of the process disclosed by Little and Marko would have been obvious, *per se*, as a matter of routine optimization. Interestingly, this directly contradicts the argument made in support of the alleged lack of enablement for determining pH in accordance with the present claims.

In any event, *per se* obviousness based on routine optimization has long since been discredited. "Reliance on *per se* rules of obviousness is legally incorrect and must cease." *In re Ochai*, 37 USPQ2d 1127, 1129 (Fed. Cir. 1995). If the prior art fails to disclose a rationale for varying parameters to be result effective, it can not have been obvious to choose the claimed parameter. *In re Antonie*, 195 USPQ 6 (CCPA 1977). Obviousness cannot be based on speculation.

The examiner should be aware that "deeming" does not discharge him from the burden of providing the requisite factual basis and establishing the requisite motivation to support the conclusion of obviousness. . . . The examiner's reference to unidentified phantom prior art techniques . . . falls short of the mark.

Ex parte Stern, 13 USPQ2d 1379, 1382 (BPA&I 1989).

Whether the changes form the prior art are "minor", as . . . [patent challenger] argues, the changes must be evaluated in terms of the whole invention, including whether the prior art provides any teaching or suggestion to one of ordinary skill in the art to make the changes that would produce the . . . [claimed] method and device.

Northern Telecom, Inc. v. Datapoint Corporation, 15 USPQ2d 1321, 1324 (Fed. Cir. 1990).

Differences between the claimed structure and the prior art structure do not amount to "an obvious design choice," when "the different structures . . . achieve different purposes." *In re Gal*, 25 USPQ2d 1076, 1078 (Fed. Cir. 1992).

Where the *optimization* of a claim variable was not recognized in the art as effecting the claimed result, the result is unobvious. *In re Antonie*, 195 USPQ 6, 8 (CCPA 1977). That a difference with the prior art amounts to an alleged "optimal condition . . . is not a substitute for some teaching or suggestion supporting an obviousness rejection." *In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993).

Moreover, routine optimization is not involved. As can be seen from the Marko citation Marko et al. discloses a two step process to isolate pure plasmid DNA. This can clearly be seen from the whole document. See for example introduction on page 382.

In this report, we describe an extension of an earlier analytical procedure 94), which allows isolation of a highly purified plasmid DNA in large quantities without the use of cesium chloride banding, ribonuclease treatment, phenol extraction, or dialysis. Extraction of lysozyme-treated bacterial cells under defined alkaline conditions selectively denatures chromosomal DNA but not CCC-plasmid DNA. When the crude alkaline extract is neutralized, high-molecular-weight chromosomal DNA aggregates to form an insoluble network; high-molecular-weight RNA and protein-SDS complexes are likewise rendered insoluble by the simultaneous addition of high concentration of salt. After removal of insoluble material by centrifugation, soluble plasmid DNA is bound to glass powder (5-7) and washed extensively with sodium perchlorate to remove remaining contaminants. Finally, highly purified DNA is recovered in high yield by elution with a low-ionic-strength buffer.

Moreover, from the detailed description for the isolation of Plasmid pBR322 DNA from *Escherichia coli* it clearly can be seen that this procedure comprises six steps including two of alkali treatment (page 383):

1. Growth of cells
2. Lysis and first alkali treatment
3. Second alkali treatment to remove residual DNA (optional)
4. 5 M Lithium chloride treatment to remove residual ribosomal RNA and single stranded DNA.
5. Proteinase K digestion (optional)
6. Final purification by adsorption to glass powder

Attention is respectfully referred to step 6. This step is the final purification step of the Marko procedure, to achieve pure plasmid DNA. Neglecting the optional steps (3 and 5) and the trivial first step, the Marko citations results in at least in a 3 step procedure.

In other words, Marko et al. do need pretreatment steps before binding the plasmid DNA onto the glass powder.

In contrast to Marko the presently claimed invention provides a method for plasmid DNA isolation from a crude bacterial lysate. This is achieved by the use of new buffer compositions which allow to selectively bind the plasmid DNA but not the chromosomal DNA on to a silica material.

The statement of rejection argues that the skilled person in the art would only have to determine the best suitable pH in the Marko procedure to arrive at the pure plasmid DNA, which can be isolated by the process of the present invention neglecting that Marko needs (a) pre-purification step(s) to extract chromosomal DNA which would possible bind also in an the silica surface in step 6.

On the contrary, Marko does not disclose any teaching with regard to the pH value because he was not faced in the last step to selectively bind plasmid DNA and not chromosomal DNA because there was no chromosomal DNA present in the mixture after Marko's pre-purification measurements. Similar to Marko et al., Little starts from a pre-purified DNA.

It is submitted that the method of Little is starting with a pre-purified DNA (for example disclosed in U.S. Patent No. 5,075,430 at col. 7, lines 19-30 and col. 8, lines 15-26). Little disclosed the following purification process:

One sample of DNA was prepared from 10 ml of overnight cultures using Triton-lysozyme lysis, followed by centrifugation of the chromosomal-membrane pellet. The supernatant was then precipitated with ethanol and dried.

In a second sample of DNA prepared from 10 ml of overnight cultures, the cells were lysed using SDS/NaOH. The mixture was then adjusted to pH 5 with a potassium acetate and centrifuged to sediment most of the chromosomal DNA along with some protein. The resulting supernatant was precipitated once with isopropanol and dried.

Three different plasmids, pBR 322, path and pRSVcat were prepared from 10 ml cultures of E. Coli HB101 cells using either the SDS/NaOH method or the rapid boiling method. Crude DNA was then purified on Celite following the procedures described hereinabove. Aliquots of the eluted purified DNA were digested with restriction endonucleases following known procedures and their concentrations estimated on an 1% agarose gel. This is in contrast to the presently claimed invention

wherein new buffer compositions were used which allow to selectively bind the plasmid DNA but not the chromosomal DNA on to a silica material.

The statement of rejection stated the point that Little, at col. 3, lines 44-48 discloses that in a high concentration of chaotropic agent the silica-containing diatomaceous earth used therein preferentially binds larger DNA over RNA and the small DNA linkers.

This step of Little's procedure is required for agarose gels that can be dissolved readily in chaotropes, such that DNA bands from gels may also be recovered.

The Little invention is a process for the immobilization of pre-purified DNA onto diatomaceous earth in the presence of a chaotropic agent. In contrast the present invention discloses a methods for plasmid DNA isolation from a crude bacterial lysate.


None of the references teaches or suggests that a binding step of circular nucleic acids under the conditions of claim 38 to silica material could be functional without any pre-purification steps. It is surprising that one single component can be directly purified from a crude mixture comprising chromosomal double stranded DNA, RNA and numerous other components, many of which are sticky. By the method of the invention, the daily routine work of a person skilled in the art working in the field of molecular cloning is improved significantly as explained above. Applicants continue to maintain that the statement of rejection relies on an "ex-post-facto" analysis, which is not allowed in making an obviousness determination under §103. *In re Deminski* 230 USPQ 313 (CCPA 1986).

Favorable action is requested.

Respectfully submitted,

JACOBSON HOLMAN PLLC

By

 22769

William E. Player
Reg. No. 31,409

400 Seventh Street, NW
The Jenifer Building
Washington, D.C. 20004
Tel. (202) 638-6666
Fax (202) 393-5350
Date: November 6, 2003
WEP/bap

C:\Documents and Settings\bperaza\Local Settings\Temp\P63712US0 amdx.txt.wpd